UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/390,740	02/17/95	COLEMAN	R

18M2/1115

BARBARA J LUTHER
INCYTE PHARMACEUTICALS INC
3330 HILLVIEW AVENUE
PALO ALTO CA 94304

EXAMINER	
REES,D	
ART UNIT	PAPER NUMBER
1807	

DATE MAILED: 11/15/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/390,740	Applicant(s) Coleman et al.
	Examiner Dianne Rees	Group Art Unit 1807

☒ Responsive to communication(s) filed on *5/3/96,7/31/96,9/3/96* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 5, 6, 13-15, 17, 18, and 21-35* is/are pending in the application.

Of the above, claim(s) *21-24, 34, and 35* is/are withdrawn from consideration.

☒ Claim(s) *1, 5, 13, 17, 18, 25, and 26* is/are allowed.

☒ Claim(s) *2, 3, 6, 14, 15, and 27-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-3, 5, 6, 13-15, 17, 18, and 21-35* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Applicant's arguments, filed 7/11/96 have been thoroughly reviewed. Rejections and /or objections not reiterated from the previous office action are hereby withdrawn. The following rejections are either newly applied or reiterated. They constitute the complete set being presently applied to the present application.Response to Applicant's arguments follows.

Election/Restriction

1. Applicant's election of Group I, (original claims 1-3,5,6,13-15,17 and 18) in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Newly submitted claims 34 and 35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims of group I which were elected are drawn to recombinant DNA molecules, expression vectors and host cells and diagnostic tests using the nucleic acids. The claims of Group III were drawn to polypeptides and are deemed separate and distinct from the invention of Group I for reasons made of record in

the previous Office Action. Having elected Group I, the Applicant cannot now add claims drawn to the invention of Group III in the present Amendment.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 34 and 35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Specification

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to teach how to make and/or use the invention, ie. as failing to provide an enabling disclosure for a diagnostic test for activated or inflammatory conditions of the pancreas, and specifically for a diagnostic test for pancreatitis, employing panec-1 and panec-2 nucleic acid probes.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in *In Re Colianni*, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986). Among these factors are: the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the breadth of the claims, the amount of direction or guidance present, and the presence or absence of working examples.

A diagnostic test is claimed for activated or inflammatory conditions of the pancreas (such as pancreatitis). The test comprises the steps of providing a biological sample, combining the biological sample with panec-1 or panec-2 nucleic acids. No additional steps are recited by which one extrapolates from detection to diagnosis in claims 2. 13. 14 and 15. Newly added claims 27-33 recite hybridization assays or PCR amplification assays wherein the amount of a hybridization complex or the presence of an "abnormal" presence of an amplified sequence is to be "correlated" positively with a condition associated with inflammation by comparison with a "standard" whose nature is unspecified.

The specification teaches the sequence of panec-1 and panec-2 and the prior art generically enables methods of determining hybridization assays using known nucleic acid sequences. However neither the art nor the specification teaches that the detection of panec-1 or panec-2 may be correlated with a disease state (the enablement required for a screening method)

and provides no evidence that a change in panec 1 or panec-2 expression will provide an indicia of a particular disease state(s) (the enablement required for a diagnostic test). Therefore neither the specification nor the prior art enables the extrapolation from detection methods to a diagnostic test.

The specification and the art teaches that panec-1 and panec-2 share sequence homologies with chemokines and that the genes are expressed in the pancreas. The specification teaches that the genes are both "highly expressed" and "specifically expressed" in the pancreas although no data is presented to allow one to judge the parameters of this statement (what degree of expression constitutes "high" expression and more importantly does "specificity" imply that the panec genes are not expressed in other tissues?) .

The specification also teaches that :

"excessive expression of either PANEC-1 or PANEC-2 **can** lead to activation of monocytes, macrophages, basophils, eosinophils, T lymphocytes and/or other cells which respond to chemokines by producing abundant proteases and other molecules which can lead to tissue damage or destruction. Therefor a diagnostic test for excess expression of PANECs **can** accelerate diagnosis and proper treatment of an abnormal condition caused by viral or bacterial infections: mechanical injury associated with trauma hereditary diseases affecting pancreatitis; biliary disease; infiltrative diseases such as leukemia and lymphomas; or other physiological and pathological problems which affect the function of the organ".

However it is not clear what the basis is for the assertion that excessive expression of PANEC 1 and 2 results in the variety of effects taught as no data is presented that the PANEC 1 and 2 products actually play a direct role in these processes; rather it appears that the role of PANEC 1 and 2 is assumed given that sequence homology indicates that the panec genes are

chemokines and chemokines are known to play pleiotropic roles in the activation of the diverse cell types described and that the diverse pathologies recited are associated with changes in the levels of chemokines. It is further noted that the art teaches that chemokines are linked to complex signal transduction pathways and that the modulatory effects of chemokines are far from understood; i.e the art is unpredictable.

Further there is no guidance in the specification to allow one to determine what constitutes an abnormal deviation in levels of panec expression and therefore what differences in levels of expression are indicative of pathology. Although the specification teaches that upregulation of PANEC expression will be associated with pathology, there is no evidence provided that this is so- as no teaching demonstrates that the pathologies listed are actually associated with panec misexpression. Since the sequences consisting of Seq IDs 1 and 3 as identified by the specification are novel, there are no analogous compounds in the prior art from which one might draw generic enablement for the claims. Given that the specification does not teach that the detection of panec-1 or panec-2 is correlated with a disease state (other than the assertion that this *may* be so) and provides no evidence that a change in panec 1 or panec-2 expression actually provides an indicia of a particular disease state(s) (again the specification only teaches that this is *possible*), the specification does not provide an adequate written description or sufficient enablement for a method of diagnosis of activated or inflammatory conditions of the pancreas and more specifically of pancreatitis. There is no description in the specification of PCR assays to be used a diagnostic test to determine abnormal levels of

PANEC-1 or 2 (i.e no support exists for newly added claims 31-32, nor is there support for the limitation of claim 33 that a primer is to be from 15-20 nucleotides and selected from the nucleic acid sequence encoding amino acid residues 93-128) as the sole description of diagnostic assays in the specification is found on page 11 which discusses a hybridization assay. The specification alludes to washing a sample which is hybridized to a nucleic acid such as panec-1 or 2 with a "compatible fluid which optionally contains a dye (or other label requiring a developer) if the nucleotide is labeled with an enzyme. The specification then states that "After the compatible fluid is rinsed off, the dye is quantitated and compared with a standard" -however nowhere in the specification is this "standard" defined and it is unclear if this standard represents a colorimetric standard used to quantify the dye intensity or reference nucleic acids from a normal individual. Either possibility is equally likely and the specification as discussed above, provides no description to enable one to determine what "standard" values are or how much deviation from standard values constitutes an "abnormal" state. As the claims recite that detection of "Abnormal levels" of hybridization complexes and is thus inclusive of detection of panec -1 and 2 DNA as well as RNA it is also unclear what an "abnormal" level of panec-1 or 2 DNA would be considered and again the complete lack of description of what actually is being measured and what is being compared provides one with no further guidance to resolve this question . The specification discusses generally that fragments of the nucleic acid sequences may be used as "PCR oligomers" however there is no description of the use of such "oligomers" in diagnostic assays, comparison of amplification products to a standard, or of specific primer sequences such

as the one claimed in newly added claim 33 (the mere fact that the sequence alignment in Figure 3 indicates that this is a nonconserved region of the sequence does not provide support for the use of this sequence as a primer as there is no suggestion anywhere in the text to use this sequence in this way)..

Therefore, given the unpredictability of the art and the lack of written description and guidance provided in the specification to enable the claims, it is the examiner's position that it would require undue experimentation for one to practice the methods of claims 2,3, 14 , 1, 27-33.

Claim Rejections - 35 USC § 112

4. Claims 2,3,14,15, 27-33 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

5. Claims 27-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a) Claim 27, for example, is indefinite in the recitation of step (a) of "a fragment thereof" as it is unclear what the metes and bounds of "a fragment" is (A single base? more than a single base?). The claim might be amended to recite a minimum range of nucleotides or to provide some functional language (such as specificity of hybridization) to establish the metes and bounds of the fragment being claimed. Similarly, the recitation of "complementary" is indefinite because it is unclear whether the sequence is fully complementary or partially complementary and, if the latter, what the degree of complementarity is. Again, the claim might be amended to overcome this rejection by reciting functional language, such as specificity of hybridization,. to establish what the degree of complementarity is (see also claim 28).

b) Claim 27 is further indefinite in the recitation of "a standard" as it is unclear how this term is defined and thus it is unclear what is actually being compared. It is also unclear what "an abnormal level" of hybridization is or what criteria determines what level is abnormal (see also claim 28)

c) Claim 31 is indefinite in the recitation of "wherein said primers comprise fragments" as it is unclear whether each primer may comprise multiple fragments and what the metes and bounds of the fragments themselves are (see above). As above, it is also unclear how a "standard" and "abnormal level" of said nucleotide sequence is defined (see also claim 32).

Claims 1,5,6, 13, 17, 18, 25 and 26 DR are allowed.

Response to Applicant's arguments:

Applicants state that they have canceled claims 2-3 and 14-15, however page 4 of Applicants' amendments direct the office to cancel claims 4,7-12, 16, 19 and 20. Accordingly claims 2-3 and 14-15 are still pending in the present application and were included in the above rejection (it is also noted that a number of nonelected claims are also still pending : 21, 23 and 24). Applicant should cancel the claims by a specific amendment if that is their intent.

Applicants state that the Examiner has no reasonable basis to doubt that the novel chemokines of the present invention would be involved in conditions related to inflammation such disease states. Applicants state that, by definition, chemokines function in inflammatory processes. Applicants contend that one of skill in the art "would have no reason to doubt that abnormal levels of PANEC-1 and PANEC-2 would be involved in conditions associated with inflammation.

The examiner has raised a number of issues that have provided a reasonable basis to doubt the enablement of the claims which recite that by detection of "abnormal levels" of Panec-1 or 2 either via detection of "hybridization complexes" which (encompass the detection of panec 1 and 2 DNA as well as RNA" or levels of amplified sequences" one will be able to diagnose a condition associated with inflammation. As. discussed above, the recitation of a "diagnostic test" requires that the method provide that for any result obtained one would be able to conclude with a low false positive rate and a low false negative rate, that an individual had a condition "associated with inflammation". Neither the specification nor the art provides any such showing for panec-1 and 2 sequences. The Examiner maintains that generic teachings concerning chemokines do not translate into a specific enablement of a diagnostic test using the specific

sequences claimed. While it is true that chemokines have a role in inflammatory processes in general, it is equally true, as stated above that their roles are pleiotropic. For any given inflammatory process, where one assesses a panel of chemokines, one invariably finds that a subset may elevated while a subset are not.In support of this, the examiner points to Rink et al. (which is cited as only one of many examples that may be found in the literature) that while certain cytokines may be elevated in an inflammatory pathology, such as Mycoplasma arthritis (for example, IL-6, IL-1, and IL-8), other cytokines, such as (IL-10 and IL-1RA) are not. Thus while IL-1,6 and 8 might be diagnostic of this particular inflammatory pathology, IL10 and IL1RA certainly would not be. It is therefor an oversimplification to suggest that the putative PANEC- proteins and nucleic acids encoding these, which are defined by virtue of their homology to other cytokines would be "expected" to be enabled as diagnostic tools. Given that it is well known that even small amino acid changes can affect protein function in unpredictable ways, it is also not found to be persuasive that a teaching made about any one chemokine would equally apply to another "homologous" chemokine.

The Applicants assert that the examiner has provided no substantive evidence that the statements of enablement of this application relating to detection methods would have been doubted by one of skill in the art or that those statements are contrary to generally accepted scientific principles.

This argument is considered but is irrelevant to the claimed invention which is not drawn to a detection method but to a method of diagnosis. The Examiner, in fact agrees with the applicant that they have enabled a method of detection. However, for reasons discussed above, in

view of the unpredicatability of the art and the lack of written description *and* the lack of guidance and the lack of working examples, the Examiner maintains that while one of skill in the art might be able to detect panec-1 and 2 nucleic acids, he or she would be unable to predictably use such results to diagnose any condition associated with inflammation.

Applicants assert that the absolute level and specificity of expression of PANEC-1, and PANEC -2 are irrelevant to claims 27-28 and 31-32 that involve comparing the amount of nucleic acid sequences detected in a sample with the amount detected in a standard, thereby determining normal levels.

This argument is considered bu t is not deemed persuasive. The lack of any description of what the standard is that one is measure, and the lack of any teaching as to what levels of hybridization of panec-1 and 2 nucleic acids or levels of amplification correlate with an "abnormal level" of panec-1 or 2, fail to enable a method of diagnosis of an inflammatory condition based on the detection of such an"abnormal level" . The lack of written description forces one to constantly guess what the applicant is intending to measure or compare; assuming *in arguendo*, that applicant's intent is that the "standard" refer to a reference nucleic acid sequence, in order to be able to perform a diagnostic method one still is required to know what the baseline for normal and abnormal expression of panec-1 and 2 during inflammation actually is. It is well settled by the courts that a patent application is not to be an invitation to do research. The applicant enables a detection method and then invites one to experiment to obtain a diagnostic test. This experimentation is undue, not because of the labor involved, but because of its unpredictable outcome. As discussed above, it is true that a general elevation of cytokines is

observed in pathological states related to inflammation, but it is far from predictable, in view of the pleotrophic roles of cytokines, which cytokine will be elevated in any particular pathology. Given that no association has been demonstrated between panec-1 or panec-2 expression and any inflammatory pathology, either by the art or by the teachings of the specification, the criteria of enablement (as defined by *Forman*, for example,) have not been met.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7401. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of the application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Dianne Rees
11/10/96

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
11/10/96